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[In the formula, A_1, A_3, and A_4 are groups indicated by hydrogen atoms, halogen, C_1 to C_5 alkyl groups, C_1 to C_5 alkoxy groups, $-COOR_1$, groups indicated by the following formula (b):

(In the formula, R_1 is a hydrogen atom, C_1 to C_5 alkyl groups.), or

groups indicated by the following formula (a):

[In the formula, R_2 is a $-CH_2OH$ group, a $-CH_2OC(O)-R_1$ group, or a $-CO_2-R_1$ group; R_3 is a $-OH$ group or $-OC(O)-R_1$ group; R_4 is a $-(CH_2)_kR_5(CH_2)_l-$ (Here, k and l are 0 or integers of 1 or more, and k+l is an integer of 10 or less.); and R_5 expresses a bond, which is a single bond (-), -CH=CH-, $-OCH_2-$, a carbonyl group, or $-CH(OH)-$.] Any one of A_1, A_3, and A_4 must always be a group indicated by the aforementioned formula (a).

A_2 is a C_1 to C_5 alkyl chain, a C_1 to C_5 alkoxy chain, a C_1 to C_5 alkenyl chain, a C_1 to C_5 hydroxyalkyl chain, or a C_1 to C_5 carbonylalkyl chain.

n, p, q, and r represent integers of 0, 1, or 2.].

Specification

A β-lactam compound, manufacturing method thereof, and serum cholesterol-lowering agents containing the same

Technical field

The present invention relates to a new β-lactam compound, manufacturing method thereof, and serum cholesterol-lowering agents containing the same.

Prior art

It is well known that hypercholesterolemia is a major risk factor for arteriosclerosis, and there have been reports about its relationship to heart disease, which is currently a high ranking cause of death (for example, Lipid Research Clinics Program, J. Am. Med. Assoc. 1984, 251, 351, and 365). In recent years, HMG-CoA reduced enzyme inhibitors have been clinically used as serum cholesterol-lowering agents. Nonetheless, although HMG-CoA reduced enzyme inhibitors have a strong effect to reduce serum cholesterol, they appear to have safety problems (for example Mevacor in Physician's Desk Reference, 49th ED, Medical Economics Date Production Company, 1995, 1584). For this reason, a highly active and safer serum cholesterol-lowering agent is being sought.

There have been reports of compounds among the natural saponins that have a serum cholesterol-lowering effect (for example, M.A. Farboodniay Jahromi et al., J. Nat. Prod., 1993, 56, 989., K. R. Price, The Chemistry and Biological Significance of Saponons in Foods and Feeding Stuffs. CRC Critical Reviews in Food Science and Nutrition, CRC Press, 1987, 26, 27). It has been inferred that these saponins lower serum cholesterol by preventing absorption of cholesterol in the small intestines (for example, P. A. McCarthy et al., J. Med. Chem., 1996, 39, 1935). Moreover, there have also been reports that β-lactam compounds reduce serum cholesterol (for example, S. B. Rosenblum et al., J. Med. Chem., 1998, 41, 973, B. Ram et al., Indian J. Chem., 1990, 29B, 1134. Merck Co. USP498, 3597).

These β-lactam compounds themselves have a mild cholesterol absorption inhibiting effect, but exhibit an even stronger cholesterol absorption inhibiting effect by receiving glucuronic acid conjugates. When administered orally, most β-lactam compounds immediately receive glucuronic acid conjugates in the process of absorption from the small intestines, become O-glucuronic acid conjugates, pass through the liver, and are excreted into the small intestine from the bile duct. These β-lactam compounds-O-glucuronic acid conjugates remain in the epithelium of the small intestine which is the site of their action, and inhibit the absorption of cholesterol (for example, M. van Heek et al., Brit. J. Pharmacol., 2000, 129, 1748, J. Pharmacol. Exp. Ther., 1997, 238, 157).

the compound indicated by General Formula (I) or pharmaceutically permissible salts thereof as the active ingredient. Further, the present invention is a serum cholesterol-lowering agent that concomitantly uses the compound indicated by General Formula (I) and β-lactamase inhibitor.

Optimum form for embodying the invention

For the pharmaceutically permissible salts of the compound indicated by the General Formula (I) of the present invention, sodium salts, and calcium salts, etc may be cited as inorganic base salts, and succinic acid, maleic acid, tosylic acid, and tartaric acid, etc may be cited as organic acid salts. The compounds of the General Formula (I) may be orally administered as is, or may be made into powder, granule, tablet, or capsule preparations using well-known preparation technology. In addition, non-oral administration is also possible in the form of administration into the rectum, suppositories and injections. The dosage will vary depending on the symptoms, age, body weight, etc of the patient, but a serum cholesterol-lowering effect may be expected, for example, by administering an adult 0.01 to 1000 mg per day divided into one to several administrations. Moreover, it appears that the serum cholesterol-lowering action is enhanced by concomitant use of the compound indicated by the General Formula (I) with β-lactamase inhibitor. β-lactamase inhibitors are drugs that prevent the decomposition of the β-lactam ring by bacteria, and clavulanic acid, etc may be used.

Examples of the compound of the present invention are indicated below, but the present invention is not limited to these. The following compounds may be cited as specific compounds included in the present invention.

(1) (4S*, 3R*)–4-{4-[(2S, 5S, 3R, 4R, 6R)-3,4,5-trihydroxy-6-(hydroxymethyl)perhydro-2H-pyran-2-yl]phenyl}-1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)propyl]azetidine-2-on

(2) (4S*, 3R*)–4-(4-{[5S, 2S, 3R, 4R, 6R)-3,4,5-trihydroxy-6-(hydroxymethyl)perhydro-2H-pyran-2-yl]methyl}phenyl)-1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)propyl]azetidine-2-on

(3) (3S, 2R, 4R, 5R, 6R)-2-[(4-{(4S*, 3R*)-1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)propyl]-2-oxoazetidine-4-yl}phenyl)methyl]-4,5-diacetyloxy-6-(acetyloxymethyl)perhydro-2H-pyran-3-yl acetate

(4) (4S*, 3R*)–4-(4-{[5S, 2R, 3R, 4R, 6R)-3,4,5-trihydroxy-6-(hydroxymethyl)perhydro-2H-pyran-2-yl]methyl}phenyl)-1-(4-chlorophenyl)-3-[3-(4-fluorophenyl)propyl]azetidine-2-on

(16) (4S*, 3R*)-4-(4-{[4S, 5S, 2R, 3R, 6R)-3,4,5-trihydroxy-6-(hydroxymethyl)perhydro-2H-pyran-2-yl]methyl}phenyl-1-phenylmethyl-3-[3-(4-fluorophenyl)propyl]-azetidine-2-on

(17) (2S, 3S, 4R, 5R, 6R)-6-[4-{(4S*, 3R*)-1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)propyl]-2-oxoazetidine-4-yl}phenylmethyl]-3,4,5-trihydroxyperhydro-2H-pyran-2-carbonic acid

(18) 2-{4-[(4S*, 3R*)-4-{[(5S, 2R, 3R, 4R, 6R)-3,4,5-trihydroxy-6-(hydroxymethyl)perhydro-2H-pyran-2-yl]methyl}phenyl-3-[3-(4-fluorophenyl)propyl]-2-oxoazetidinyl]phenoxy}-2-methylpropionic acid ethyl ester

(19) 2-{4-[(4S*, 3R*)-4-{[(5S, 2R, 3R, 4R, 6R)-3,4,5-trihydroxy-6-(hydroxymethyl)perhydro-2H-pyran-2-yl]methyl}phenyl-3-[3-(4-fluorophenyl)propyl]-2-oxoazetidinyl]phenoxy}-2-methylpropionic acid

(20) 2-{4-[(4S*, 3R*)-4-{[(5S, 2R, 3R, 4R, 6R)-3,4,5-trihydroxy-6-(hydroxymethyl)perhydro-2H-pyran-2-yl]methyl}phenyl-3-[3-(4-methylphenyl)propyl]-2-oxoazetidinyl]phenoxy}-2-methylpropionic acid ethyl ester

(21) 2-{4-[(4S*, 3R*)-4-{[(5S, 2R, 3R, 4R, 6R)-3,4,5-trihydroxy-6-(hydroxymethyl)perhydro-2H-pyran-2-yl]methyl}phenyl-3-[3-(4-methylphenyl)propyl]-2-oxoazetidinyl]phenoxy}-2-methylpropionic acid

(22) (4S, 3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl-4-(4-{[(2S, 5S, 3R, 4R, 6R)-3,4,5-trihydroxy-6-(hydroxymethyl)perhydro-2H-pyran-2-yl]methyl}phenyl)-1-(4-fluorophenyl)azetidine-2-on

(23) (4S, 3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-{[(2S, 5S, 3R, 4R, 6R)-3,4,5-trihydroxy-6-(hydroxymethyl)perhydro-2H-pyran-2-yl]methyl}phenyl)-1-phenylazetidine-2-on

(24) (4S, 3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-{[(2S, 5S, 3R, 4R, 6R)-3,4,5-trihydroxy-6-(hydroxymethyl)perhydro-2H-pyran-2-yl]methyl}phenyl)-1-(4-methylphenyl)azetidine-2-on

(25) (4S, 3R)-4-(4-{[(5S, 2R, 3R, 4R, 6R)-3,4,5-trihydroxy-6-(hydroxymethyl)perhydro-2H-pyran-2-yl]methyl}phenyl)-1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)propyl]azetidine-2-on

(26) (4S, 3R)-4-(4-{[(2S, 5S, 3R, 4R, 6R)-3,4,5-trihydroxy-6-(hydroxymethyl)perhydro-2H-pyran-2-yl]methyl}phenyl)-1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-oxopropyl]azetidine-2-on

(38) (4S, 3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-1-(4- {[(2S, 5S, 3R, 4R, 6R)-3,4,5-trihydroxy-6-(hydroxymethyl)perhydro-2H-pyran-2-yl]methyl}phenyl)-4-(4-fluorophenyl)azetidine-2-on

(39) (4S, 3R)-3-[(3S)-3-(4-{[(2S, 5S, 3R, 4R, 6R)-3,4,5-trihydroxy-6-(hydroxymethyl)perhydro-2H-pyran-2-yl]methyl}phenyl)-3-hydroxypropyl]-1-phenyl-4-(4-fluorophenyl)azetidine-2-on

(40) (3R*, 4R*)-4-(4-{[5S, 2R, 3R, 4R, 6R)-3,4,5-trihydroxy-6-(hydroxymethyl)perhydro-2H-pyran-2-yl]methyl}phenyl-3-[3-(4-fluorophenyl)propyl] -1-(4-fluorophenyl)azetidine-2-on

(41) 3-((3S)-3-hydroxy-3-phenylpropyl)(4S, 3R)-4-(4-{((5S,3R,4R,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)perhydro-2H-pyran-2-yl]methyl}phenyl)-1-phenylazetidine-2-on

(42) 4-[3-(3S)-3-(4-fluorophenyl)-3-hydroxypropyl](4S, 3R)-4-(4-{(2S, 5S, 3R, 4R, 6R)-3,4,5-trihydroxy-6-(hydroxymethyl)perhydro-2H-pyran-2-yl]methyl}phenyl)-2-oxoazetidinyl]benzoic acid ethyl ester

(43) 4-(4-{(5S, 2R, 3R, 4R, 6R)-3,4,5-trihydroxy-6-(hydroxymethyl)perhydro-2H-pyran-2-yl]methyl}phenyl)(4S, 3R)-1-(4-methylphenyl)-3-[3-(4-fluorophenoxy)ethyl]-azetidine-2-on

(44) 3-(3-phenylpropyl)(4S, 3R)-4-(4-{(5S,3R,4R,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)perhydro-2H-pyran-2-yl]methyl}phenyl-1-phenylazetidine-2-on

(45) (4S, 3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-{[(2S, 5S, 3R, 4R, 6R)-3,4,5-trihydroxy-6-(hydroxymethyl)perhydro-2H-pyran-2-yl]ethene}phenyl-1-(4-fluorophenyl)azetidine-2-on

(46) (4S, 3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-{[(2S, 5S, 3R, 4R, 6R)-3,4,5-trihydroxy-6-(hydroxymethyl)perhydro-2H-pyran-2-yl]ethyl}phenyl-1-(4-fluorophenyl)azetidine-2-on

(47) (4S, 3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-{[(2S, 5S, 3R, 4R, 6R)-3,4,5-trihydroxy-6-(hydroxymethyl)perhydro-2H-pyran-2-yl]-1-propene-3-yl}phenyl-1-(4-fluorophenyl)azetidine-2-on

(48) (4S, 3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-{[(2S, 5S, 3R, 4R, 6R)-3,4,5-trihydroxy-6-(hydroxymethyl)perhydro-2H-pyran-2-yl]propyl}phenyl-1-(4-fluorophenyl)azetidine-2-on

(49) 3-((3S)-{4-[(2S, 5S, 3R, 4R, 6R-)-3,4,5-trihydroxy-6-(hydroxymethyl)perhydro-2H-pyran-2-yl]phenyl}-3-hydroxypropyl)(4S, 3R)-1,4-bis(4-fluorophenyl)azetidine-2-on

Table 1

1. Compound No.
2. Structural Formula

Table 3

1. Compound No.
2. Structural Formula

Table 5

1. Compound No.
2. Structural Formula

Table 7

1. Compound No.
2. Structural Formula

Table 9

1. Compound No.
2. Structural Formula

Table 11

1. Compound No.
2. Structural Formula

Examples of manufacturing the compounds indicated by General Formula (I) of the present invention are cited below.

Manufacturing Example 1

(1) Example of manufacturing a compound in which R^4 in the General Formula (I) is $-CH^2-$.

(a) Using a departure source material of the Compound (1-2) obtained by allowing a Tebbe reactant (for example, T. V. Rajanbabu et al., J. Org. Chem., 1986, 51, 5458) to act on tetrabenzyl glucuronolacton (1-1), a Suzuki coupling reaction (for example, C. R. Johnson et al., Synlett, 1997, 1406) is conducted with the Compound (1-3), and then the compound indicated by the Compound (1-4) is obtained by a desilylation reaction.

[Key]
1. Tebbe reactant
2. 9-BBN(9-borabicyclo[3,3,1]nonane
3. TBAF=n-tetrabutylamoniumfloride

(b) The compound indicated by the aldehyde Compound (1-5) is obtained by oxidizing the hydroxy group of the Compound (1-4).

(c) The compound indicated by the imine Compound (1-7) is obtained by allowing the aldehyde Compound (1-5) and the amine Compound (1-6) to condense in the presence of molecular sieves and tosylic acid (TsOH).

[Key]
1. 1) Base, thermal reflux

(d) The Compound (1-10) is obtained by acetylation of the Compound (1-9).

[Key]
1. Acetylation reaction

(2) Example of manufacturing a compound in which R_4 in the General Formula (I) is $-CH_2-$.

The Compound (1-13) is obtained by allowing a Grignard reagent (1-12) to react on the Compound (1-11) (for example, M. F. Wong et al., J. Carbohydr. Chem., 1996, 15(6), 763, C. D. Hurd et al., J. Am. Chem. Soc, 1945, 67, 1972, H. Togo et al., Synthesis, 1998, 409). Or, the Compound (1-13) is obtained by a catalytic reaction after allowing the Grignard reagent (1-12) to react with the Compound (1-1) in the same way, or after making into an olefin either by using triethylsilylhydride to remove the hydroxide group produced, or by processing with a tosyl group or a base as a free group, such as halogen, etc. After using the Grignard reagent to allow Mg to act on the Compound (1-13), the Compound (1-14) is obtained when allowing DMF (dimethylformaldehyde) to react, or the

A Grignard reagent (2-3) is allowed to react with the Compound (1-11), to make a well-known Compound (2-4) (for example, F. Marquez et al., An. Quim., Ser. C., 1983, 79(3), 428).

(Here, X is the same as previously described.)

The methyl group of the Compound (2-4) is converted to aldehyde to become the Compound (1-14) (for example, P. S. Portoghese et al., J. Med. Chem., 2000, 43, 2489).

The Compound (2-2) is obtained when using $NaBH_4$ to reduce the Compound (1-14)

Manufacturing Example 3

(1) An example of manufacturing a compound in which R_4 in the General Formula (I) is $-OCH_2-$.

(a) A Mitsunobu reaction is conducted between the Compound (3-1) and the Compound (3-2) obtained by well-known methods (for example, D. Zhai et al., J.

lithium hydroxide to hydrolyze the ester part. The General Formula (I) is obtained by de-protection of the Compound (4-3).

[Key]
1. Or, then
2. (Here, R=OH)
3. De-protection
4. General Formula (I)

Manufacturing Example 5

Example of manufacturing a compound in which R_2 in the General Formula (I) is $-CO_2H$.

The Compound (5-2) when oxidizing the Compound (5-1) using TEMPO (2,2,6,6-tetramethyl-1-piperidenyloxy, free radical).

Manufacturing Example 6

The Compound (6-3) was made by thioglycosylation of the compounds (6-1) and (6-2). After oxidizing the Compound (6-3) into a sulfone, a Ramberg-Backlund reaction (for example, P. S. Belica et al., Tetrahedron Lett., 1998, 39, 8225, and F. K. Griffin et al., Tetrahedron Lett., 1998, 39, 8179) was conducted to make the Compound (6-4). After conducting a catalytic reaction on the Compound (6-4), TBAF was allowed to act on this to make the Compound (1-4). The Compound (1-4) is the synthesis material to obtain the General Formula (I) following the Manufacturing Example 1.

(Here, X is the same as previously described. Z represents a free group such as halogen, $-OC(O)CF_3$, $-O-C(=NH)CCl_3$, etc.)

(2) Example of manufacturing a compound in which R_3 of the General Formula (I) is –OH, $-OC(O)R_1$.

The Compound (7-7) is made by de-protecting the Compound (7-6) obtained in the same way as in Manufacturing Example 7-(1) described above. After one of the hydroxide groups of the Compound (7-7) is made into a Tf group, the Compound (7-3) is obtained by allowing carburation in the presence of carbon monoxide (for example R. E. Dolle et al., Chem. Commun., 1987, 904). The Compound (7-3) is a synthesis raw material used to obtain the General Formula (I) by following the Manufacturing Examples 1 and 3.

[Key]
1. Lewis acid
2. De-protection
3. Base

Moreover, there is also a method of using the Compound (7-11). After conducting coupling in the same way as in the Compound (1-11), the Compound (7-3) is made by conducting a haloform reaction of the acetyl group (Ac) (for example, S. Kajigaeshi et al., Synthesis, 1985, 674).

The Compound (8-3) is made by conducting a Boc reaction of the amino group in the Compound (8-2).

After making the Compound (8-4) by carborating the carbonic acid part of the Compound (8-3) following the W. W. Ogilvie et al. method (Bioorg. Med. Chem., 1999, 7, 1521), the Compound (8-5) is made by removing the Boc.

β-lactam (8-6) is made by cyclization of the Compound (8-5) obtained in this way into β-lactam following the W. W. Ogilvie et al. method (Bioorg. Med. Chem., 1999, 7, 1521).

After allowing an N-alkylation reaction of the β-lactam Compound (8-6) following the method of Dominic M.T. Chan, et al. (Tetrahedron Lett., 1998, 39, 2933), the Compound (8-12) is made by de-benzylation based on a catalytic reaction.

The Compound (8-13) is made by allowing a Suzuki reaction of the glucose derivative (1-2) with the Compound (8-12) following the method of C. R. Johnson et al. (Synlett, 1997, 1406).

After allowing LDA to act on the Compound (8-13), the Compound (8-14) is made by allowing methyl acrylate to act on this, and conducting a C-alkylation reaction.

After making the ester part of the Compound (8-14) an acid chloride, the Compound (8-16) is made following the method of E. Negishi et al. (Tetrahedron Lett., 1983, 24, 5181).

Further, A_1 in the General Formula (I) is a compound of the following formula (a):

and, for example, the Compound (39) can be synthesized using the following formula (8-23):

to react with the Compound (8-15) following the Manufacturing Example 8. Moreover, A_4 in the General Formula (I) is a compound of the following formula (a):

[Key]
1. De-protection
2. General Formula (I)

Manufacturing Example 10

Example of manufacturing as an optically active substance (III)

The compound indicated by the Compound (9-3) is obtained by condensing the compounds (10-1) and (9-2) using the method of E.J. Corey et al. (Tetrahedron Lett., 1991, 32, 5287). The General Formula (I) is obtained by de-protecting the Compound (9-3)

The Compound (8-15) can be obtained from the Compound (11-6) using the same method as in Manufacturing Example 8.

(11-6) is a synthesis source material to obtain the General Formula (I) following the Manufacturing Example 8. Moreover, when using the Compound (11-7) instead of the Compound (11-4), the Compound (11-8) is obtained corresponding to the Compound (11-6) by using the same methods.

Moreover, the Compound (12-3) is obtained by conducting a catalytic reaction of the Compound (12-2). The Compound (12-3) thus obtained is a synthesis source material to obtain General Formula (I) following the Manufacturing Example 8.

Manufacturing Example 13

The Compound (13-2) is obtained by using the Compound (13-1) (R_6 is –Me, -Br, $-CH_2OTBS$), and conducting C-glycosylation (for example, K. C, Nicolaou et al., J. Chem. Soc. Chem. Comm., 1984, 1153) on the Compound (1-11) in the presence of a Lewis acid ($BF_3 \cdot OEt_2$, $ZnCl_2$, AgOTf, etc). After converting the R_6 of the Compound (13-2) to aldehyde in the same way as in Manufacturing Example 1-(1)-(6), Manufacturing Example 1-(2), or Manufacturing Example 2-(2), this becomes a synthesis source material to obtain the General Formula (I) following the Manufacturing Example 1.

[Key]
1. 1) Reduction
2. 2) Halogenation
3. Cyclization

Manufacturing Example 16

It is possible to obtain the Compound (16-1) by using a Heck reaction to couple the Compound (12-1) and the Compound (15-3) in the same way as in the Manufacturing Example 12. It is possible to convert the Compound (16-1) to the General Formula (I) following the Manufacturing Example 17.

Manufacturing Example 17

Lithium hydroxide, etc is used to remove the camphor sultam in the Compound (17-1) making the Compound (17-2) (the camphor sultam can be recovered and reused). Then, the General Formula (I) is obtained either by allowing this Compound (17-2) to react in a non-solvent such as phosphorus oxychloride, or in a solvent such as methylene chloride or dichloroethane, or by allowing the

[Key]
1.Esterification
2. Cyclization
3. General Formula (I)
4. (R_7: expresses Me, Et.)

Manufacturing Example 18

After making the Compound (18-2) either by conducting an oxide reaction of the Compound (18-1) using selenium dioxide, etc, or by using an oxidation method such as $Pd(OAc)_2$-benzoquinone-perchloric acid on the Compound (18-4), the Compound (18-3) is obtained by conducting an asymmetric reduction of the ketone part in the same way as in the Manufacturing Example 8. Moreover, the Compound (18-3) can be obtained by conducting hydroboration on the Compound (18-4), and a stereo selective reaction can be conducted using an asymmetric borane reducing agent, etc.

material to obtain the General Formula (I) following the Manufacturing Example 8.

[Key]
1. Catalytic asymmetric reduction
2. β-lactamization
3. Pd catalyst
4. Pd catalyst or Ni catalyst
5. (R_7 is a –OAc group or –OBn group.)

Manufacturing Example 20

The Compound (20-2) is made by an asymmetric reduction of the imine (20-1) following the Manufacturing Example 19. After making the corresponding carbonate by hydrolyzing the ester part of the Compound (20-2), the Compound (19-3) is obtained by using a condensing agent to make a β-lactam (for example DCC). The Compound (19-3) may also be obtained by making a β-lactam of the Compound (20-2) (for example, EtMgBr). The Compound (19-3) is a source material to obtain the General Formula (I) following the Manufacturing Example 19.

[Key]
1. Asymmetric reduction
2. Hydrolysis of the ester group
3. β-lactamization

Manufacturing Example 21

After allowing a base to act on the Compound (19-1), the Compound (21-2) is made by adding the Compound (21-1). The Compound (21-5) is made either by making the Compound (21-4) by asymmetric reduction of the Compound (21-2), or by allowing the Compound (21-3) to act on the Compound (21-2). The Compound (21-6) is obtained by allowing the Compound (21-3) to act on the Compound (21-4). Then, after making the Compound (21-8) by coupling the Compound (21-6) and the sugar part (12-1[sic] or 19-5), β-lactam (21-10) is obtained. On the other hand, after making the Compound (21-7) by asymmetric reduction of the Compound (21-5), the Compound (21-9) is made by coupling with the sugar part. The Compound (21-10) is obtained by making a β-lactam of the Compound (21-9). The Compound (20-10) obtained in this way is a source material for the General Formula (I).

Further, A_1, A_2, A_4, R_3, R_4, p, q, r, and Z in the chemical formulae indicated in Manufacturing Examples 1 to 21 are the same as previously described, and R_6 is either $-CH=CH_2$, or $-CH_2OH$. k is an integer of one or more, l is zero or an integer of one or more, and k+l is an integer of ten or less.

Test example

An example of a pharmacological test of the serum cholesterol lowering action on hamsters is cited below.

Lipid-lowering action in cholesterol-feed-loaded hamsters

Hamsters were divided into groups of three, and were given feed containing 0.5% cholesterol (CE-2, CLEA Japan) for four days. The test compounds were orally administered by forced feeding once per day at the same time as beginning the cholesterol loading. 0.2 mL corn oil per 100 g body weight only (control group) or a solution of the test compound in corn oil was administered. Twenty hours after the final administration, blood was sampled from the abdominal aorta under mild ether anesthesia, and serum was isolated. The serum total cholesterol was measured using the cholesterol E-test Wako (Wako Pharmaceuticals). The results of the test compound are indicated by the control percentage (%) in relation to the increase portion of serum cholesterol concentration based on high cholesterol loading. Further, the pharmacological action of the compounds listed under light rotation in Tables 1 to 12 were measured as optically active substances. Those results are indicated in the following table. The numbers in Table 13 represent the change percentage (%) in relation to the control group, and therefore the negative numbers indicate positive cholesterol lowering action.

Enzyme: α-N-acetyl-D-galactosaminidase manufactured by Yariika 0.32 units (0.5 m sodium citrate buffer solution containing 1.69 unit/m 10.1% BSA)

Solvent: citric acid buffer solution (pD=3) 0.6 mL

Temperature: 35° C

Procedures: Two milligrams of standard substance were weighed and placed in an NMR sampling tube, and 0.6 mL of sodium citrate buffer solution and 0.32 units of enzyme were added. This was left to stand at 35° C, and the NMR was measured at six time intervals.

The basic substance residual percentage (%) of the results of these tests are indicated in the following Table 14.

Table 14

Time / Standard substance	2	4	6	8	10	12	18	24
B	89	79	68	57	50	45	40	22
A	100	100	100	100	100	100	100	100

As is clear from this table, in contrast to the rapid hydrolysis and decomposition of 78% of the O-aryl substance (B) used as a comparison in 24 hours, it was confirmed, as predicted, that the C-aryl substance (A), which aims for metabolic stability and converts ether bonds to carbon-carbon bonds, was unaffected by the enzymes, and that no decomposition products were created at all in the following 24 hours.

Embodiments

The present invention is explained in further detail using embodiments, but the present invention is in no way limited by these embodiments.

Embodiment 1

4-(4-{[(5S, 2R, 3R, 4R, 6R)-3,4,5-trihydroxy-6-(hydroxymethyl)-perhydro-2H-pyran-2-yl]methyl}phenyl) (4S*, 3R*)–1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)propyl]azentidine-2-on (Compound (2))

Synthesis of Compound (2)

(I) Molecular sieve (3.46 g), tosylic acid (catalytic volume), and P-fluroanaline (0.61 mL) were added to a toluene solution (54.0 mL) of the Compound (1-5) (3.46 g), and thermal reflux was conducted for 1.5 hours. The insoluble substance was removed by sieve, the filter solution was enriched, and the following reaction was used.

(II) nBu_3N (5.1 mL) was added to a toluene solution of the compound obtained in (I). 5-(4-fluorophenyl)penthane acid chloride (1.16 g) was added, and after conducting thermal reflux for 15 hours, 1N HCl solution (15 mL) was added and agitated for 15 minutes. The organic layer was rinsed with saturated sodium bicarbonate water and saturated saline solution, dried with Glauber's salt and the organic layer was enriched under reduced pressure. The residue was used in the following reaction.

(III) 10% Pd-C (200 mg) was added to a mixed solution of MeOH: THF = 5 mL : 1 mL in the compound obtained in (II), and this was agitated for five hours at room temperature under hydrogen gas flow. This was filtered using celite, the filter solution was enriched, and 64 mg (yield 26%) of the Compound (2) was obtained by purifying using silica gel column chromatography (chloroform: methanol = 10 : 1).

Mass (ESI) m/z:	554 $(M+H_2O)^+$
IR (KBr):	3376, 1737, 1503, 1218 cm^{-1}
^{1}H-NMR (CD_3OD):	1.82 to 1.98 (m, 4H), 2.65 to 2.78 (m, 3H), 3.09 to 3.39 (m, 7H), 3.64 (dd, J= 5.4, 12.2 Hz), 3.77 to 3.81 (m, 1H), 4.94 to 4.98 (m, 1H), 6.98 to 7.05 (m, 4H), 7.18 to 7.22 (m, 2H), 7.30 to 7.33 (m, 4H), 7.38 (d, J= 7.8 Hz, 2H)

Embodiment 2

4-(4-{[(5S, 2R, 3R, 4R, 6R)-3,4,5-triacetoxy-6-(acetoxymethyl)-perhydro-2H-pyran-2-yl]methyl}phenyl) (4S*, 3R*)–1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)propyl]azentidine-2-on (Compound (3))

The Compound (XI) produced by allowing nBuLi (10 mL, 1.57 M hexane solution) to act on p-(tert-butyldiphenylsyloxylmethyl)-bromobenzine (6.66 g) at –78° C, was titrated into tetrabenzylglucuronolactam (I) (7.31 g) at –78° C after agitating for two hours, the organic layer was extracted using ethyl ester acetate, rinsed with saturated saline solution, and dried with Glauber's salt. The solvent was removed under pressure reduction, and the residue was used in the following reaction.

The compound obtained was dissolved in methylene chloride (26 mL), Et_3SiH (0.82 mL), and $BF_3 \cdot Et_2O$ (0.33 mL) were added at –50° C, and this was agitated for 1.5 hours. Saturated sodium bicarbonate water was added, and after agitating for one hour, the organic layer was removed with diethyl ether, rinsed with saturated saline solution, and dried with Glauber's salt. This was purified using silica gel column chromatography (ethyl acetate : hexane = 1 : 3), and 1.48 mg of the Compound (2-2) (yield 15%) was obtained.

IR (KBr):	3388, 1452, 1362, 1210, 1068, 1026 cm^{-1}
^{1}H-NMR ($CDCl_3$):	3.49 to 3.81 (m, 4H), 4.04 to 4.96 (m, 13H), 6.92 to 6.95 (m, 2H), 7.09 to 7.76 (m, 2H)

Reference Example 3-a: Synthesis of the Compound (3-a)

4-(2,3,4,6-tetra-o-benzyl-β-D-glucopyranosyl)methoxybenzoic acid methyl ester (Compound (3-a))

Mass (ESI) m/z: 684 $(M+H+Na)^+$
IR (neat): 3442 cm^{-1}
^{1}H-NMR ($CDCl_3$): 1.56 (s, 1H), 3.49 to 3.53 (m, 1H), 3.60 to 3.77 (m, 6H), 4.08 to 4.12 (m, 1H), 4.20 to 4.23 (m, 1H), 4.52 to 4.61 (m, 6H), 4.85 (ABq, J= 11.2 Hz, 2H), 4.93 (s, 2H), 6.88 (d, J= 8.8 Hz, 2H), 7.15 to 7.36 (m, 22H)

Reference Example 3-c: synthesis of the Compound (1-14)

4-(2,3,4,6-tetra-o-benzyl-β-D-glucopyranosyl)benzaldehyde (Compound (1-14))

(I) 0.9 g of NBS and 0.05 g of benzoylperoxide were added to 3 mL of a carbontetrachloride solution with 0.3 g of 4-(2,3,4,6-tetra-o-benzyl-β-D-glucopyranosyl)toluene, and thermal reflux was conducted for two hours. The reaction solution was cooled, 30 mL of diethyl ether was added, crystals were filtered out, and the filter solution was enriched. This was purified using silica gel column chromatography (ether ester acetate : hexane = 1 : 8).

(II) $NaHCO_3$ (45 mg) was added to a DMSO (3 mL) solution of the bromo substance (224 mg) obtained from (I), and this was agitated for one hour at room temperature, and four hours at 100° C. After extracting the reaction solution using ethyl ester acetate (30 mL), and after rinsing the organic layer with saturated saline solution, this was dried using sodium sulfate anhydride. When removing the solvent, the Compound (1-14) was obtained as a brown oily substance at a yield of 26% (two processing runs).

Mass (m/e): 436 (M^+), 394, 307, 273, 245, 214, 163, 135, 105, 77, 51, (BP)
IR (neat): 2914, 1641, 1437, 1257, 1017, 954, 708 cm^{-1}
^{1}H-NMR ($CDCl_3$, 400 MHz)
δ: 1.96, 1.97, 2.06 (12H, eaeh, s), 3.75 – 5.40 (7H, m), 7.96, 8.02 (4H, ABq),10.06 (1H, s)

Embodiment 3

methanol = 5 : 1), 377 mg of the Compound (19) (yield 51% (3 runs)) was obtained.

Mass (ESI) m/z: 636 $(M-H)^-$
IR (KBr): 3400, 1722, 1503 cm^{-1}
^{1}H-NMR (CD_3OD): 1.53 (s, 6H), 1.81 to 1.95 (m, 4H), 2.65 to 2.68 (m, 2H), 2.72 to 2.78 (m, 1H), 3.09 to 3.41 (m, 7H), 3.62 to 3.66 (m, 1H), 3.77 to 3.82 (m, 1 H), 4.81 (d, J= 2.0 Hz, 1H), 6.85 (d, J= 9.3 Hz, 2H), 6.97 to 7.02 (m, 2H), 7.18 to 7.22 (m, 4H), 7.30 (d, J= 7.8 Hz, 1H), 7.38 (d, J= 8.3 Hz, 2H)

Embodiment 4

6-[(4-{(2S*, 3S*)-1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)propyl]-4-oxoazetidine-2-yl}(2S, 3S, 4R, 5R, 6R)- 3,4,5-trihydroxyperhydro-2H-pyran-2-carboxilic acid (Compound (17))

Saturated sodium bicarbonate water (6.6 mL) and NaOCl (6.6 mL) were added to an acetone nitryl (6.6 mL) solution of the Compound (2) (300 mg), TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy, free radical) (10 mg), and KBr (10 mg), and this was agitated for three hours at room temperature. The organic layer was extracted using ethyl ester acetate. The organic layer was rinsed with saturated saline solution, and dried with Glauber's salt. After removing the organic solvent, this was purified using silica gel column chromatography (chloroform : methanol = 10: 1), and 90 mg of the Compound (17) (yield 29.4%) was obtained.

Mass (ESI) m/z: 566 $(M-H)^-$
IR (KBr): 3388, 1737, 1509 cm^{-1}

Triethylamine (16.4 mL) and (Boc) 2O (13.5 mL) were added to a THF-water (140 mL) suspension of 12.53 g of the Compound (8-2) while icing, and this was agitated for four hours at room temperature. The THF was removed under pressure reduction and the residue aqueous layer was adjusted to pH 4 using 10% citrate aqueous solution. The ethyl ester acetate (100 mL x 3) was extracted; the extracted solution was rinsed with water (100 mL x 3) and saturated saline solution (100 mL x 1), and was dried using sodium sulfate anhydride. The solvent was removed, and 17.4 g (assayed) of the Compound (8-3) was obtained.

Mass m/z:	357 (M^+), 331, 301,283, 256, 212, 148, 120, 91(base)
IR (KBr):	3298, 2968, 1791, 1656, 1608, 1506, 1452, 1392, 1242, 1161 cm^{-1}
^{1}H-NMR ($CDCl_3$):	1.23 (s, 9H), 5.05 (bs, 3H), 6.94 (d, J=8.3 Hz, 2H), 7.32 to 7.41 (m, 8H)

Reference Example 4-c: Synthesis of the Compound (8-4)

(3S)-3-[4-(benzyloxy)phenyl]-3-[(t-butoxy)carbonylamino]propionic acid benzyl ester (Compound (8-4))

Triethylamine (5.9 mL), and isobutylchlorformate (5.8 mL) were added to a THF (80 mL) solution of 14.4 g of the Compound (8-3) while icing, and after agitating for 40 minutes, CH_2N_2/Et_2O (prepared from N, N-dimethylnitrosourea (30 g), Et_2O (100 mL) and 40% KOH aqueous solution (100 mL)) were added and agitated for 1.5 hours. After using AcOH to decompose the excess diasomethane, and after dissolving everything by adding ether (100 mL) and water (100 mL), this was

^{1}H-NMR ($CDCl_3$): 3.05 (dd, J=6.4 Hz, 18.3 Hz, 1H), 3.27 (dd, J=6.4 Hz, 16.8 Hz, 1H), 4.64 to 4.65 (m, 1H), 4.94 to 5.03 (m, 4H), 6.89 (d, J=8.7 Hz, 2H), 7.15 to 7.41 (m, 12H), 8.77 to 8.78 (m, 3H)

Reference Example 4-e: synthesis of the Compound (8-6)

(4S)-4 -[4-(benzyloxy)phenyl]azetidine-2-on (Compound (8-6))

Water (15 mL) was added to an ethyl ester acetate suspension solution of the Compound (8-5) (6.48 g), and made into an alkali using 1M-K_2CO_3 aqueous solution. Extracting with ethyl ester acetate (30 mL x 2), the extraction solution was rinsed with saturated saline solution (50 mL x 1), and dried with sodium sulfate anhydride. The solvents were removed; the residue was dissolved in 60 mL of benzene. 3.6 mL of triethylamine and 2.7 mL of trimethylsilylchloride were added and agitated for 14 hours at room temperature. After celite filtering of the reaction solution and removal of the filter solution, the residue was dissolved in 65 mL of ether, 10.7 mL of 2M-t-butyl magnesium chloride - ether was added while icing and was agitated for 18 hours at room temperature. The reaction solution was iced, saturated ammonium chloride aqueous solution (50 mL), ethyl ester acetate (50 mL), and 10% HCl aqueous solution (50 mL) were added and agitated for one hour at room temperature. The organic layer was separated, and the water layer was further extracted using ethyl ester acetate (50 mL x 1). The combined organic layer was rinsed with water (50 mL x 1), saturated sodium bicarbonate water (50 mL x 1) and saturated saline solution (50 mL x 1), and was dried using sodium sulfate anhydride. The solvents were removed; the residue was purified using silica gel column chromatography (chloroform : acetone = 10 : 1), and after rinsing the crystals obtained using ethyl ester acetate : hexane, 2.50 g of the Compound (8-6) (yield 60.7%) was obtained when drying.

Mass m/z: 253 (M^+), 162, 91(base), 65
IR (KBr): 3184, 1749, 1698, 1540, 1410, 1248, 1100 cm^{-1}
^{1}H-NMR ($CDCl_3$): 2.84 to 2.88 (ddd, J=1.0 Hz, 2.4 Hz, 15.1 Hz, 1H), 3.39 to 3.44 (ddd, J=2.4 Hz, 5.4 Hz, 14.8 Hz, 1H), 4.68 (dd, J=4.9 Hz, 14.9 Hz, 1H), 5.08 (s, 2H), 6.09 (bs, 1H), 6.97 (dd, J=2.9 Hz, 7.8 Hz, 2H), 7.28 to 7.44 (m, 7H)

0.20 g of 5% palladium-carbon was added to an ethyl ester acetate-methanol (50 mL) solution of the Compound (8-26) (2.00 g), and was agitated for nine hours at room temperature in an H_2 gas atmosphere. After the reaction solution was celite filtered and the filter solution removed, the residue was purified using silica gel column chromatography (chloroform : acetone = 10:1) and 1.36 g of the Compound (8-27) (yield 91.9%) was obtained.

Mass m/z:	257 (M^+), 214, 210 (base), 91, 58
IR (KBr):	3106, 1707, 1620, 1503, 1453, 1383, 1257, 1218 cm^{-1}
^{1}H-NMR ($CDCl_3$):	2.93 (dd, J=2.4 Hz, 15.7 Hz, 1H), 3.52 (dd, J=5.9 Hz, 15.2 Hz, 1H), 4.94 (dd, J=2.9 Hz, 5.4 Hz, 1H), 5.22 (s, 1H), 6.85 (d, J=8.3 Hz, 2 H), 6.93 (s, J=8.8 Hz, 2 H), 7.23 to 7.27 (m, 4H)

Reference Example 4-h: Synthesis of the Compound (8-28)

4-[(2S)-1-(4-fluorophenyl)-4- oxoazetidine-2-yl]phenyltrifluoromethane sulfonate (Compound (8-28))

0.12 mL of pyridine, and 0.26 mL of trifluoromethane sulfonate anhydride were added to a suspension of the Compound (8-27) (0.35 g) in 10 mL of methylene chloride while icing, and the reaction solution was agitated for one hour. The reaction solution was poured into ice water (20 mL), and extraction was conducted with ethyl ester acetate (30 mL x 2). The extraction solution was rinsed with 10% HCl aqueous solution (20 mL x 1), saturated sodium bicarbonate water (40 mL x 1) and saturated saline solution (30 mL x 1), and was dried using sodium sulfate anhydride. The solvents were removed, and when purifying the

Reference Example 4-j: Synthesis of the Compound (8-30)

3-{(4S, 3R)-4-[4-({2S, 5S, 3R, 4R, 6R}-6-[(benzyloxymethyl)-3,4,5-tribenzyloxy)perhydro-2H-pyran-2-yl]methyl)phenyl]-1-(4-fluorophenyl) oxyazetidine-3-yl}propionic acid methyl ester (Compound (8-30))

2M-LDA/heptane-THF (1.3 mL) was diluted with 3 mL of THF, and a THF (1.5 mL) solution with 1.00 g of the Compound (8-29) was added at -78° C and agitated for one hour. THF (2 mL) solution with 0.132 g of methyl acrylate was then added, and agitated for 0.5 hours. Saturated ammonium chloride water (30 mL) was added, and the reaction solution was returned to room temperature. Extraction was conducted with ethyl ester acetate (60 mL x 2). After rinsing the extraction solution with saturated saline solution (50 mL x 1) and drying using sodium sulfate anhydride, the solvents were removed. When purifying the residue using silica gel column chromatography (ethyl ester acetate : n-hexane = 1:4), 0.793 g of the Compound (8-30) (yield 71.8%) was obtained.

Mass (ESI) m/z:	864 $(M+1)^+$
IR (KBr):	2854, 1740, 1509, 1452, 1362, 1215, 1140, 1098 cm^{-1}
^{1}H-NMR ($CDCl_3$):	2.19 to 2.23 (m, 2H), 2.47 to 2.59 (m, 2H), 2.72 (dd, J=8.8 Hz, 14.6 Hz, 1H), 3.04 to 3.13 (m, 2H), 3.30 to 3.37 (m, 2H), 3.42 to 3.48 (m, 1H), 3.64 (s, 3H), 3.61 to 3.74 (m, 4H), 4.47 to 4.63 (m, 5H), 4.81 to 4.94 (m, 4H), 6.90 (t, J=8.8 Hz, 2H), 7.15 to 7.35 (m, 26H)

Reference Example 4-k: Synthesis of the Compound (8-31)

(4S, 3R)-4-[4-({(2S, 5S, 3R, 4R, 6R}-6-[(benzyloxy)methyl]-3,4,5-tribenzyloxy)perhydro-2H-pyran-2-yl]methyl)phenyl]-1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-oxopropyl] azetidine-2-on (Compound (8-31))

^{1}H-NMR ($CDCl_3$): 2.23 to 2.42 (m, 2H), 2.72 (dd, J+8.8 Hz, 14.7 Hz, 1H), 3.09 to 3.74 (m, 11H), 4.46 to 4.63 (m, 4H), 4.66 (d, J=2.5 Hz, 1H), 4.81 to 4.94 (m, 4H), 6.91 (J=8.8 Hz, 2H), 7.11 (t, J=8.3 Hz, 2H), 7.33 to 7.89 (m, 26H), 7.96 to 8.00 (m, 2H)

Embodiment 5

(4S, 3R)-4-(4-{[(2S, 5S, 3R, 4R, 6R)-3,4,5-trihydroxy-6-(hydroxymethyl) perhydro-2H-pyran-2-yl}methyl}phenyl]-1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-oxopropyl]azetidine-2-on (Compound (26))

1M-BBr_3/methylene chloride solution (1.8 mL) was added to a methylene chloride (5.4 mL) solution with the Compound (8-31) (0.27 g) at -78° C, and the reaction solution was agitated for one hour. The reaction solution was poured into ice water (30 mL), and extraction was conducted using chloroform (30 mL x 3). The extraction solution was rinsed using water (50 mL x 1), saturated sodium bicarbonate water (50 mL x 1), and saturated saline solution (50 mL x 1), and was dried using sodium sulfate anhydride. The solvents were removed, and when purifying the residue using silica gel column chromatography (chloroform : methanol = 8:1), 0.147 g of the Compound (8-26) (yield 89.1%) was obtained.

Mass (ESI) m/z: 568 $(M+1)^+$
IR (KBr): 3400, 2902, 1737, 1680, 1596, 1506, 1386, 1224, 1152, 1134, 1086 cm^{-1}
^{1}H-NMR (CD_3OD): 2.28 to 2.34 (m, 2H), 2.74 (dd, J=8.3 Hz, 14.6 Hz, 1H), 3.09 to 3.39 (m, 10H), 3.64 (dd, J=5.3 Hz, 11.7 Hz, 1H), 3.78 (dd, J=2.4 Hz, 11.7 Hz, 1H), 4.95 (d, J=2.4 Hz, 1H), 7.01 to 7.05 (m, 2H), 7.22 to 7.26 (m, 2H), 7.27 to 7.38 (m, 6H), 8.06 to 8.10 (m, 2H)

Embodiment 6

3-[3(S)-3-(4-fluorophenyl)-3-hydroxypropyl-(4S, 3R)-4-(4-{[(2S, 5S, 3R, 4R, 6R)-3,4,5-trihydroxy-6-(hydroxymethyl)perhydro-2-pyran-2-yl]methyl}phenyl)-1-(4-fluorophenyl)azetidine-2-on (Compound (22))

2M-LDA/heptane-THF (0.6 mL) was diluted with THF (1.5 mL), added to 3 mL of a THF solution with 0.336 g of the Compound (8-29) at -78° C, and agitated for 30 minutes. Then, 1.8 mL of DMPU (1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone) was added and agitated a further 30 minutes. After adding 1.5 mL of THF solution with 0.111 g of 4-fluorocinnamylbromide to the reaction solution and agitating for 30 minutes, saturated ammonium chloride solution (30 mL) was added, and the reaction solution was returned to room temperature. Extraction was conducted using ethyl ester acetate (50 mL x 2). The extraction solution was rinsed using water (50 mL x 3) and saturated saline solution (50 mL x 1) and was dried using sodium sulfate anhydride. The solvents were removed, and when purifying the residue using silica gel column chromatography (ethyl ester acetate : n-hexane = 1:5), 0.253 g of the Compound (8-33) (yield 64.4%) was obtained.

Mass (ESI) m/z:	934 $(M+Na(23))^+$
IR (KBr):	2890, 1746, 1509, 1383, 1359, 1224, 1137, 1098 cm^{-1}
^{1}H-NMR ($CDCl_3$):	2.63 to 2.88 (m, 3H), 3.12 (dd, J=1.9 Hz, 14.7 Hz, 1H), 3.20 to 3.38 (m, 4H), 3.47 to 3.48 (m, 1H), 3.59 to 3.74 (m, 5H), 4.45 to 4.63 (m, 4H), 4.65 (d, J=2.4 Hz, 1H), 4.81 to 4.94 (m, 4H), 6.12 (dt, J=6.8 Hz, 14.6 Hz, 1H), 6.45 (d, J=14.7 Hz, 1H), 6.90 (t, J=8.8 Hz, 2H), 6.95 (t, J=8.7 Hz, 2H), 7.14 to 7.35 (m, 28H)

Embodiment 8

Synthesis of Compound (25)

4-(4-{[(5S, 2R, 3R, 4R, 6R)-3,4,5-trihydroxy-6-(hydroxymethyl)perhydro-2H-pyran-2-yl]methyl}phenyl)-(4S, 3R)-1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)propyl]azetidine-2-on (Compound (25))

agitated for one hour at room temperature. The reaction solution was poured into saturated ammonium chloride water (40 mL), and extraction was conducted using ethyl ester acetate (50 mL x 2). The extraction solution was rinsed using saturated saline solution (50 mL x 1), and this was dried using sodium sulfate anhydride. The solvents were removed and when purifying the residue using silica gel column chromatography (chloroform : acetone = 40:1) and (ethyl ester acetate : n-hexane = 1:2), 1.30 g of the Compound 11-3 (yield 91.8%) was obtained.

Mass m/z:	343 (M^+), 312, 279, 129 (base), 101
IR (KBr):	2944, 1720, 1689, 1440, 1413, 1389, 1335, 1215, 1050 cm^{-1}
^{1}H-NMR (CD_3OD):	0.97 (s, 3H), 1.16 (s, 3H), 1.35 to 1.41 (m, 2H), 1.87 to 2.12 (m, 7H), 2.39 (t, J=8.3 Hz, 2H), 2.78 (t, J=7.4 Hz, 2H), 3.46 (q, J=4.4 Hz, 2H), 3.67 (m, 3H), 3.85 to 3.88 (m, 1H)

Reference Example 5-b: Method of synthesizing the Compound (11-10)

(4R)-4-{(1S) (4-bromophenyl[(4-fluorophenyl)amino]methyl)-5- (4-aza-10,10-dimethyl-3-dioxo-3-thiatricyclo[5,2,1,01, 5]decan-4-yl)-5-oxopentane methyl ester acid (Compound (11-10))

$Ti(OiPr)_4$ (0.2 mL) was added to a methylene chloride (10 mL) solution of $TiCl_4$ (0.23 mL) while icing, and was agitated for 15 minutes. A methylene chloride (3.5 mL) solution with 0.65 g of the Compound (11-3) was added and agitated for five minutes. Then, after agitating diisopropylethylamine (0.72 mL) for one hour, this was cooled to -20° C, a methylene chloride (3.5 mL) solution with 1.15 g of (1z)-aza-2-(4-bromophenyl)-1-(4-fluorophenyl) ether was added and agitated for three hours. Acetate-methylene chloride (1 mL + 5 mL) was added to the reaction solution, and returned to room temperature. A 10% hydrochloric acid aqueous solution (30 mL) was added, and extraction was conducted using ethyl ester acetate (50 mL x 2). The extraction solution was rinsed using water (50 mL x 1), saturated sodium bicarbonate water (50 mL x 1) and saturated saline solution (50 mL x 1), and was dried using sodium sulfate anhydride. The solvents were removed, and when purifying the residue using silica gel column

Reference Example 6: Synthesis of the Compound (12-4)

3-{[(4S, 3R)-4-[4-(3-{(2S, 5S, 3R, 4R, 6R)-6-(benzyloximethyl)-3,4,5-(tribenzyloxy)perhydro-2H-pyran-2-yl}-1-propene)phenyl]-1-(4-fluorophenyl) oxoazetidine-3-yl]propionic acid methyl ester (Compound (12-4))

575 mg of the Compound (11-11) and 1. 2 g of 3-(2,3,4,6-tetra-o-benzyl-β-D-glucopyranosyl)-1-propene was dissolved in trimethyl amine (5 mL), tri-o-trylphosphine (43 mg) and palladium acetate (16 mg) were added in an Ar atmosphere, and agitated for 13 hours at 100° C. After returning to room temperature and filtering out the insolubles, the filter solution was diluted with ethyl ester acetate (50 ml), rinsed with 10% hydrochloric acid and saturated saline solution, and dried using sodium sulfate anhydride. The solvents were removed, and when purifying the residue using silica gel column chromatography (ethyl ester acetate : n-hexane = 1:4), 1.1 g of the Compound (12-4) (yield 87.0%) was obtained.

Mass (ESI) m/z:	890 $(M+1)^+$
IR (neat):	3016, 2896, 1741, 1503, 1371, 1215, 1092, 831, 747 cm^{-1}
^{1}H-NMR ($CDCl_3$):	2.23 (q, J=7.8 Hz, 2H), 2.44 to 2.60 (m, 4H), 3.11 (m, 1H), 3.33 to 3.44 (m, 3H), 3.58 to 3.75 (m, 4H), 3.66 (s, 3H), 4.54 to 4.94 (m, 9H), 6.38 (m, 2H), 6.91 to 7.32 (m, 28H)

The compound obtained is a synthesis intermediate for obtaining the General Formula (I) following Reference Examples 4-(l), (j), (k) and Embodiments 5, 6, 7, and 8.

Reference Example 7: Synthesis of the Compound (50)

(4S, 3R)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-{[(2S, 5S, 3R, 4R, 6R)-3,4,5- trihydroxy-6-(hydroxymethyl)perhydro-2H-pyran-2-yl]methoxypropyl-3-yl}phenyl-1-(4-fluorophenyl)azetidine-2-on (Compound (50))

Reference Example 8-a: Synthesis of the Compound (19-6)

(3R)-3-(4-bromophenyl)-3-hydroxy-N-phenylpropane amide (Compound (19-6))

RuCl2 [(S)-BINAP] (dichloro[S]-(-) 2,2'bis-(diphenylphosphino)-1,1'-binaphthyl) ruthenium (II) catalyst (12 mg) was added to an ethanol-methylene fluoride solution (3:1, 4 mL) of 3-(4-bromophenyl)-3-oxo-N-phenylpropane amide (950 mg), and was agitated for six hours while allowing a catalytic asymmetric hydride reaction to occur at 100° C, 5 At (under a hydrogen gas flow). After cooling the reaction solution to room temperature, when enriching, filtering out deposited crystals and drying, 725 mg of the Compound (19-6) (yield 76%, asymmetric yield 99% e.e.) was obtained.

m.p. = 210 to 212° C

$[\alpha]_D$:	+33.0 (C=1.0, THF)
Mass (m/z):	319(M^+), 183, 157, 135, 93(BP)65
IR(KBr):	3316, 1614, 1599, 1530, 1443, 1368, 1065, 693 cm^{-1}
^{1}H-NMR(DMSO):	2.69 (dd, J=4.4 Hz, 14.2 Hz, 1H), 2.77 (dd, J=8.8 Hz, 14.2 Hz, 1H), 5.16 (n, 1H), 5.69 (d, J=4.4 Hz, 1H), 7.14 (t, J=7.3 Hz, 1H), 7.40 (d, J=7.8 Hz, 2H), 7.46 (d, J=8.3 Hz, 2H), 7.64 (d, 8.3 Hz, 2H), 7.69 (d, J=7.8 Hz, 2H)

Compound (19-8) (1.0 g) was added to a THF-HMPA solution (3:1, 4 mL) with Zn(Cu) (106 mg), and thermal reflux was conducted for three hours. After adding palladium acetate (1.7 mg), and 2-(di-tert-butylphophino)biphenyl (4.4 mg) to the reaction solution at 0° C and agitating for five minutes, the Compound (19-7) (223 mg) was added. After cooling the reaction solution to room temperature, 10% hydrochloric acid aqueous solution (50 mL) and ethyl ester acetate (30 mL), the insolubles were filtered. The filter solution was extracted was using ethyl ester acetate (50 mL x 2), rinsed with saturated saline solution (50 mL), and dried using sodium sulfate anhydride. The solvents were removed, and when purifying using silica gel column chromatography (ethyl ester acetate : hexane = 1:4), 480 mg of the Compound (19-9) was obtained as a colorless crystal (yield 84.3%).

m.p. = 95 to 97° C

$[\alpha]_D$:	-61.2 (C=1.0, $CHCl_3$)
ESI-MS(m/z):	796 $(M+Na)^+$, 774 $(M+1)^+$
IR(KBr):	2854, 1749, 1599, 1497, 1452, 1371, 1212, 1068 cm^{-1}
^{1}H-NMR($CDCl_3$):	1.71 to 1.75 (m, 1H), 2.04-2.10 (m, 1H), 2.63 to 2.74 (m, 1H), 2.81 to 2.87 (m, 1H), 2.94 (dd, J=2.4 Hz, 15.1 Hz, 1H), 3.18 to 3.22 (m, 1H), 3.29 (t, J=13.1 Hz, 1H), 3.36 to 3.40 (m, 1H), 3.53 (dd, J=5.9 Hz, 15.1 Hz, 1H), 3.59 to 3.75 (m, 4H), 4.55 to 4.66 (m, 4H), 4.80 to 4.88 (m, 4H), 4.96 to 4.98 (m, 1H), 7.02 (t, J=6.8 Hz, 1H), 7.14 to 7.37 (m, 28H)

Possibility of industrial utilization

New β-lactam compounds of the present invention having C-saponins in the molecule, which are stable in relation to metabolism based on glucocidase, and hydrolosis by bases or acids, have a strong serum cholesterol-lowering action, and are useful as serum cholesterol-lowering agents.

A_2 is a C_1 to C_5 alkyl chain, a C_1 to C_5 alkoxy chain, a C_1 to C_5 alkenyl chain, a C_1 to C_5 hydroxyalkyl chain, or a C_1 to C_5 carbonylalkyl chain.

n, p, q, and r represent integers of 0, 1, or 2.].

2. A manufacturing method of a compound or a pharmaceutically permissible salt thereof indicated by the General Formula (I), wherein

a compound indicated by the General Formula (II)

(In the formula, A_1, A_2, R_3 and p are the same as described above, X is a free group such as halogen, or an optically active sultam derivative.), and

a compound indicated by the General Formula (III)

(In the formula, A_3, A_4, R_3, n, q and r are the same as described above.)

are allowed to undergo a Staudinger reaction or a Mannich reaction.

3. A manufacturing method of a compound or a pharmaceutically permissible salt thereof indicated by the General Formula (I), wherein

a compound indicated by the General Formula (IV)

(In the formula, n, p, q, r, A_1, A_2, A_3, A_4, and R_3 are the same as described above.)

5. A manufacturing method of a compound or a pharmaceutically permissible salt thereof indicated by the General Formula (VII)

(In the formula, A_1, A_2, A_4, R_3, n, p, q, and r, are the same as described above. R_7 is a single bond (-), 1CH=HC-, or $-OCH_2$. k is an integer of 1 or more; l is 0 or an integer of 1 or more; and k+l is an integer of 10 or less.),

wherein a coupling reaction is allowed between a compound indicated by the General Formula (VIII)

(In the formula, A_1, A_2, A_4, R_3, n, p, q, and r are the same as described above. Z expresses a free group such as a halogen atom or a triflate group, and k is 0 or an integer of 1 to 10.) and

a compound indicated by the General Formula (IX)

Corrected Claims

[Accepted on July 15, 2002 (15.07.02) by the International Office: Claim 1 of the present application was corrected. The other claims were not changed. (2 pages)]

1. A compound or a pharmaceutically permissible salt thereof indicated by the General Formula (I)

[In the formula, A_1, A_3, and A_4 are groups indicated by hydrogen atoms, halogen, C_1 to C_5 alkyl groups, C_1 to C_5 alkoxy groups, $-COOR_1$, groups indicated by the following formula (b):

(In the formula, A_1, A_2, and R_3 are the same as described above, X is a free group such as halogen, or an optically active sultam derivative.), and

a compound indicated by the General Formula (III)

(In the formula, A_3, A_4, R_3, n, q and r are the same as described above.)

are allowed to undergo a Staudinger reaction or a Mannich reaction.

3. General Formula (IV)

In the compound described in Claim 1 of Cited Literature WO97/16455, if G is one of the groups (b), (c), or (e), G is bonded by a oxygen to carbon bond (-O-G). Specifically, this is an O-glycoside (O-saponin) of a β-lactam compound.

The two differ on this point.

(2) Moreover, in the compound of Claim 1 of the present application, when k and l of R_4 are 0 and R_5 is $-OCH_2-$, the carbon atoms on both sides of the oxygen atom that forms the tetrahydropyran ring are both bonded to the oxygen atom through carbon atoms. Specifically, this is a C-glycoside (C-saponin) of a β-lactam compound. On the other hand, when G described in Claim 1 of Cited Literature WO97/16455 is a compound of group (d), one of the carbon atoms on both sides of the oxygen atom that forms the tetrahydropyran ring is bonded to an oxygen atom. Specifically, this is an O-glycoside (O-saponin) of a β-lactam compound. The compound of Claim 1 of the present application differs from the compound in which G is group (d) as described in Claim 1 of Cited Literature WO97/16455. (Refer to the following diagram.)

weaker pharmacological effect and a shorter duration because the O-glycosides, which are the active members of the compound, are easily hydrolyzed by the glycosidase and bases, etc. present in the small intestines, specifically, by metabolism within the body.

On the other hand, the C-glycosides of the of the β-lactam compounds of Claim 1 of the present application are stable in relation to glycosidase and bases, and therefore can be expected to resolve the problems of weak pharmaceutical action of short duration that β-lactam compounds with O-glycosides have.

(3) As described above, the C-glycosides of the of the β-lactam compounds of Claim 1 of the present application can be expected to have superior biological stability and a greater pharmaceutical effect than the O-glycosides of the β-lactam compounds described in Claim 1 of Cited Literature WO97/16455.

4. Moreover, Claims 2 to 5 of the present application indicate methods of synthesizing the β-lactam compounds of Claim 1 of the present application using C-glycosides as the base substance. The cited literature does not describe methods of synthesis using C-glycoside as the base substance, nor is this even implied.

(End)